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Alexis L Perry
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Vassilis I. Zannis et al.	Art Unit:	1636
Serial No.:	09/827,854	Examiner:	Nguyen, Q.
Filed:	April 5, 2001	Customer No.:	21559
Title:	COMPOUNDS AND METHODS FOR LOWERING CHOLESTEROL LEVELS WITHOUT INDUCING HYPERTRIGLYCERIDEMIA		

Mail Stop Amendment
Commissioner for Patents
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DECLARATION OF DR. VASSILIS I. ZANNIS, M.D.
UNDER 37 C.F.R. § 1.132

I, VASSILIS I. ZANNIS, declare:

1. I am a named inventor of the subject matter claimed in United States Patent Application Serial No. 09/827,854 filed on April 5, 2001.

2. I attended the University of California at Berkley where I obtained a Ph.D. in Biochemistry. I am currently a Professor in the department of Medicine and Biochemistry and the Director of Molecular Genetics at the Whitaker Cardiovascular Institute associated with the Boston University School of Medicine. My education and professional experience are detailed in the attached curriculum vitae.

3. I have read and understood the Office Action, dated September 19, 2005. This Declaration is presented to overcome the rejection of claims 30-31, 33-34, 36-37, 43-44, 46-47, 51, 53-62, and 64-72 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

4. The methods of the invention have been used successfully and predictably in animals that lack an endogenous, normally functioning apoE, e.g., apo-E deficient mice, as well as in animals that possess an endogenous, normally functioning apoE, e.g., wild-type mice. The data that is included with this Declaration, discussed below, demonstrate the expression of a secreted apoE polypeptide lacking amino acids 260-299 in wild-type and apoE-deficient animals, and the ability of the secreted apoE polypeptide to clear cholesterol in these animals without inducing hypertriglyceridemia following intravascular administration of a recombinant adenoviral vector encoding the apoE polypeptide.

5. Our results indicate that expression of a secreted apoE polypeptide lacking amino acids 260-299 in animals that express a normally functioning low density lipoprotein (LDL) receptor always produces a therapeutic effect, regardless of the presence or absence of a normally functioning apoE polypeptide.

6. The supporting data are as follows:

(a) We have shown that administration of apoE2-202 (a.a. 1-202 of apoE2) to knock-in mice where the endogenous mouse apoE was replaced by the human apoE2 cleared transiently the high cholesterol levels of the knock-in mice and also reduced their high triglyceride levels (see Fig. 1).

(b) We have also found that injection of full-length apoE in normal mice C57BL/6 that express the endogenous mouse apoE induces high cholesterol and high triglyceride levels (Fig. 2). Co-injection of these mice with a mixture containing a similar dose of a full-length apoE (apoE2 or apoE4) along with truncated apoE (apoE2-202 or apoE4-202 (a.a. 1-202 of apoE4)) prevents the induction of dyslipidemia. This result occurs because the truncated apoE has a

dominant effect and clears the lipoprotein remnants that would otherwise have accumulated due to the presence of full-length apoE alone (see Fig. 2).

(c) We have also demonstrated the ability of variously truncated apoE polypeptides, expressed in apoE-deficient mice, to reduce cholesterol levels without inducing hypertriglyceridemia for several days following infection of the mice with a recombinant adenovirus encoding the truncated apoE polypeptide (see Fig. 3).

(d) We have also demonstrated the ability of truncated apoE polypeptides to clear cholesterol without inducing hypertriglyceridemia in mice that have an apoA-I mutant instead of their endogenous apoA-I. Expression of a mutant human apoA-I, designated apoA-I[E110A/E111A] by adenovirus-mediated gene transfer, causes hypertriglyceridemia and moderated hypercholesterolemia in apoA-I-deficient mice. Simultaneous expression of the mutant apoA-I [E110A/E111A] and a truncated apoE4-202 corrected the dyslipidemia (see Fig. 4).

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Respectfully submitted,

Date: 2/21/2006

Vassilis I Zannis

Vassilis I. Zannis, M.D.